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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/737,476	12/18/2000	Leo G.J. Frenken	P 0275850 T 7060C	9341

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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	**PAPER NUMBER**
1638	
MAIL DATE	**DELIVERY MODE**
07/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/737,476	FRENKEN ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16* is/are pending in the application.

4a) Of the above claim(s) *8 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's submission filed on May 14, 2007 has been entered.

Claims 14-15 are cancelled.

Claims 1-13 and 16 are pending.

Claims 8 and 10-13 are withdrawn.

Claims 1-7, 9 and 16 are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 103

Claims 1-4, 6-7 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over any of Magnuson et al. (Enhanced recovery of a secreted mammalian protein from suspension culture of genetically modified tobacco cells. Protein Expression and Purification, 1996, Vol. 7, pages 220-228) or Casterman et al. I (WO 94/04678, 3 March 1994, Applicant's IDS) or Casterman et al. II (US Patent No. 5,759,808, issued June 2, 1998), in view of Owen et al. (Synthesis of a functional anti-phytochrome single-chain Fv protein in transgenic tobacco. Biotechnology, Vol. 10, pages 790-794, July 1992), Moloney M.M. et al. (Subcellular targeting and purification of recombinant proteins in plant production systems. Biotechnol Genet Eng Rev. 1997;14:321-36. Review), Herrera-Estrella L. et al. (US Patent No. 5,728,925, issued March 17, 1998) and Hilton J.R. (An association of phytochrome with the chloroplast envelope membranes

of *Spinacia oleracea* L.: a preliminary observation. New Phytol., 1983, Vol. 95, pages 175-178), for the reasons of record set forth in the office action mailed November 14, 2006.

Applicant's arguments filed May 14, 2007 have been fully considered but they are not persuasive.

Applicants maintain that Moloney does not teach production of antibodies in plants or targeting of antibodies to the plastids of plants, and point out that the reference of Moloney is a review article discussing subcellular targeting and purification of recombinant proteins in plants. Applicants maintain that the reference does not disclose the production of functional heavy chain antibodies or fragments thereof in plants or the targeting of heavy chain antibodies or fragments thereof to the plastids of plants. (reply page 5)

The Examiner maintains that Moloney was not cited for teaching the production of functional heavy chain antibodies or fragments thereof in plants; Magnuson et al. Casterman I. et al. and Casterman II. et al. were cited for teaching the production of functional heavy chain antibodies or fragments thereof in plants (page 4 of the Office Action mailed November 14, 2006). Moloney M.M. et al. teach the targeting of recombinant proteins to the chloroplast as a means to alter genetic and biochemical functions within the chloroplast (page 5 of the Office Action mailed November 14, 2006). In this regard it is also noted that a functional heavy chain antibody or fragment thereof is both a recombinant protein, and a means to alter genetic and biochemical functions within the chloroplast when it is specific for an antigen required for a genetic or biochemical function that occurs within the chloroplast.

Applicants also maintain that Herrera-Estrella does not teach production of functional heavy chain antibodies or fragments thereof in plants or the targeting of these antibodies to the plastids of plants, as while Herrera-Estrella discloses chimeric DNA sequences encoding a transit peptide and a polypeptide heterologous to the transit peptide for transport of the polypeptide into the chloroplast of a plant, Herrera-Estrella does not teach or suggest expression of functional heavy chain antibodies or fragments thereof in plants. (reply page 6)

The Examiner maintains that Herrera-Estrella was not cited for teaching the production of functional heavy chain antibodies or fragments thereof in plants; Magnuson et al. Casterman I. et al. and Casterman II. et al. were cited for teaching the production of functional heavy chain antibodies or fragments thereof in plants (page 4 of the Office Action mailed November 14, 2006). Herrera-Estrella L. et al. was cited for teaching a DNA sequence also including a sequence which expresses a peptide which targets a heterologous protein to a plant chloroplast, and that that the heterologous protein may consist of any protein or peptide sought to be introduced into the chloroplasts of determined plants (page 5 of the Office Action mailed November 14, 2006). In this regard it is also noted that a functional heavy chain antibody or fragment thereof is a protein that is heterologous to a plant.

Applicants additionally maintain that that Magnuson, Casterman I, Casterman II, and Owen suggest that an ER targeting sequence is required for expression of functional antibodies in plants, and that these references thus teach away from the present invention of targeting a functional heavy chain antibody or a fragment thereof to the plastid of a plant. Applicants

maintain that since Magnuson, Casterman I, Casterman II, and Owen require an ER targeting sequence for the production of functional heavy chain antibodies, there is no motivation to combine the teachings of the cited references, and there is no reasonable expectation of success in making the necessary modifications to the teachings of the cited references for obtaining the claimed invention. (reply pages 5-6)

With respect to Magnuson, Casterman I, Casterman II, and Owen using an ER targeting sequence, it is noted that the pending claims do not exclude the use of an ER targeting sequence. It is also noted that Magnuson, Casterman I, Casterman II, and Owen do not teach that an ER targeting sequence is necessary to produce functional antibodies in plants. Accordingly, that Magnuson, Casterman I, Casterman II, and Owen used an ER targeting sequence does not teach away from the instant invention.

Applicants maintain that Hilton does not teach production or subcellular targeting of proteins in plants, as Hilton only discloses that phytochromes are associated with the chloroplast envelope membranes. Applicants maintain that Hilton does not disclose production of antibodies in plants or targeting of antibodies to the plastids of plants. Applicants also point out that phytochromes and heavy chain antibodies are structurally and functionally distinct molecules. Thus, there is no motivation to combine the teachings of Hilton, the cited references which teach expression of heavy chain antibodies in plants, and the cited references that teach production of proteins in plants. (reply page 6)

The Examiner maintains that Hilton J.R. was not cited for teaching the production or subcellular targeting of proteins in plants; Hilton J.R. was cited for teaching an antigen that is a

protein present in a plant chloroplast, as required by the rejected claims, i.e. Hilton J.R. was cited for teaching the localization of phytochrome in plastids and chloroplasts (page 5 of the Office Action mailed November 14, 2006). The teaching of Hilton J.R. that the protein phytochrome is localized in plastids and chloroplasts provides motivation for one skilled in the art to produce and target to plant chloroplasts a heavy chain immunoglobulin or active fragment thereof binds to a phytochrome protein present in a plant chloroplast. It is also noted that the chloroplast envelope membranes of a chloroplast are a part of the chloroplast.

Claims 1-5, 7, 9 and claim 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over any of Magnuson et al. (Enhanced recovery of a secreted mammalian protein from suspension culture of genetically modified tobacco cells. Protein Expression and Purification, 1996, Vol. 7, pages 220-228) or Casterman et al. I (WO 94/04678, 3 March 1994, Applicant's IDS) or Casterman et al. II (US Patent No. 5,759,808, issued June 2, 1998), in view of Le Gall et al. (Engineering of a single-chain variable-fragment (scFv) antibody specific for the stolbur phytoplasma (Mollicute) and its expression in Escherichia coli Applied and Environmental Microbiology, Vol. 64, No. 11, pages 4566-4572, November 1998), Moloney M.M. et al. (Subcellular targeting and purification of recombinant proteins in plant production systems. Biotechnol Genet Eng Rev. 1997;14:321-36. Review), Herrera-Estrella L. et al. (US Patent No. 5,728,925, issued March 17, 1998) and Rohozinski J. et al. (Do light-induced pH changes within the chloroplast drive turnip yellow mosaic virus assembly? J Gen Virol. 1996 Feb;77 (Pt 2):163-5), for the reasons of record set forth in the office action mailed November 14, 2006.

Applicant's arguments filed May 14, 2007 have been fully considered but they are not persuasive.

Applicants point to the deficiencies of Magnuson, Casterman I, Casterman II, Moloney, and Herrera-Estrella discussed above. Applicants also maintain that Le Gall and Rohozinski do not cure the deficiencies of Magnuson, Casterman I, Casterman II, Moloney, and Herrera-Estrella. Applicants point out that Le Gall does not teach production of functional heavy chain antibodies or fragments thereof in plants and targeting the antibodies to the plastids of the plants. or a DNA molecule that includes a sequence encoding a peptide for targeting the heavy chain antibodies or fragments thereof to the plastids of a plant. Applicants also point out that Le Gall specifically indicates that the vector for expressing scFv contains the leader sequence pelB which would express the scFv through the secretory (ER) pathway, and that Le Gall neither teaches nor suggests expressing antibodies in the plastids of a plant. Applicants maintain that Le Gall teaches away from the instant invention as it suggests that an endoplasmic reticulum targeting sequence is necessary to produce functional antibodies in plants. (reply pages 6-7)

The Examiner maintains that Magnuson, Casterman I, Casterman II, Moloney, and Herrera-Estrella are not deficient as discussed above. The Examiner also maintains that Le Gall was not cited for teaching the production of functional heavy chain antibodies or fragments thereof in plants, or for teaching subcellular targeting of heavy chain antibodies to the plastids of the plants. Le Gall et al. was cited for teaching a method for modifying a tobacco plant to produce an anti-stolbur phytoplasma antibody (pages 8-9 of the Office Action mailed November 14, 2006). The teachings of Le Gall et al. that expressing in a plant a DNA sequence encoding a single-chain Fv recombinant immunoglobulin capable of specific binding with an antigen that is

a stolbur phytoplasma plant pathogen will produce transgenic plants protected against phytoplasma infection provide one skilled in the art a reasonable expectation of success that a heavy chain immunoglobulin or active fragment thereof can be produced in a plant and bind to a plant pathogen present in a plant. With respect to Le Gall's use of a pelB leader sequence, it is noted that the pending claims do not exclude the use of an endoplasmic reticulum targeting sequence. It is also noted that Le Gall et al. do not teach that an endoplasmic reticulum targeting sequence is necessary to produce functional antibodies in plants. It is additionally noted that the subcellular location of the plant pathogen bound by Le Gall' antibodies, a stolbur phytoplasma, requires targeting of the antibody to a different subcellular location (sieve tubes within the phloem) than the plant pathogen bound by the antibody in the rejected claims (subcellular location = chloroplast). Accordingly, Le Gall's use of a pelB leader sequence does not teach away from the instant invention.

Applicants also point out that Rohozinski does not teach production of functional heavy chain antibodies or fragments thereof in plants and targeting the antibodies to the plastids of the plants, and that Rohozinski teaches that the assembly of TYMV occurs within the intermembrane space of chloroplasts. Applicants maintain that Rohozinski neither teaches nor suggests the production of functional heavy chain antibodies or fragments thereof in plants, and that Rohozinski does not teach or suggest subcellular targeting of heavy chain antibodies to the plastids of the plants. (reply page 7)

The Examiner maintains that Rohozinski J. et al. was not cited for teaching the production of functional heavy chain antibodies or fragments thereof in plants, or for teaching

subcellular targeting of heavy chain antibodies to the plastids of the plants. Rohozinski J. et al. was cited for teaching the localization of turnip yellow mosaic virus plant pathogen in chloroplasts (page 9 of the Office Action mailed November 14, 2006). The teachings of Rohozinski J. et al. that some plant pathogens such as the turnip yellow mosaic virus may be localized in chloroplasts provide motivation for one skilled in the art to produce and target to plant chloroplasts a heavy chain immunoglobulin or active fragment thereof binds to a plant pathogen present in a plant. It is also noted that the intermembrane space of a chloroplast is a part of the chloroplast.

Double Patenting

Claims 1-7, 9 and 16 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11-12 of copending Application No. 11/267,191, filed November 7, 2005, for reasons of record.

Applicants respectfully point out that this is a provisional obviousness-type double patenting rejections between two applications and point to MPEP 804 (I)(B) which indicates that if a provisional double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection. Applicants maintain that MPEP 804 (I)(B) applies given the amendments made to claim 1 addressing the previous rejections under 35 U.S.C. 102(b), 35 U.S.C. 112 (second paragraph) and 35 U.S.C. 103(a).

The rejection is maintained, as the provisional double patenting rejection is not the only rejection remaining.

Claims 1-7, 9 and 16 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11-12 of copending Application No. 11/267,310, filed November 7, 2005, for reasons of record.

Applicants respectfully point out that this is a provisional obviousness-type double patenting rejections between two applications and point to MPEP 804 (I)(B) which indicates that if a provisional double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection. Applicants maintain that MPEP 804 (I)(B) applies given the amendments made to claim 1 addressing the previous rejections under 35 U.S.C. 102(b), 35 U.S.C. 112 (second paragraph) and 35 U.S.C. 103(a).

The rejection is maintained, as the provisional double patenting rejection is not the only rejection remaining.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cynthia Collins
Primary Examiner
Art Unit 1638

CC

Cynthia Collins
7/23/07